BIOLITEC®

CERALAS™ I 689 nm

DIODE LASER SYSTEM

USER'S MANUAL

Important: Before operating this system, read this manual thoroughly!

Manual LA-0788 REV F

Biolitec, Inc., 515 Shaker Rd., East Longmeadow, MA 01028, USA
Telephone: 413 525 0600, Fax: 413 525 0611

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Radiancy, Inc., 515 Shaker Rd., East Longmeadow, MA 01028 USA
Telephone: 413.525.0000 Fax: 413.525.0011

WARNINGS

CLASS IIIb LASER PRODUCT

DIODE LASER 689 nm ± 3 nm Continuous Wavelength 0.5 W (MAX)

DIODE LASER 635 nm ± 10 nm Continuous Wavelength 1 mW (MAX)

EN 60825-1 **EN 60601-2-22**

DANGER-VISIBLE LASER RADIATION-AVOID EYE OR SKIN EXPOSURE TO DIRECT OR SCATTERED RADIATION!

The optical power output from this system can cause severe eye damage or other injuries. Exercise extreme caution to prevent injury. Only trained qualified personnel familiar with the operating parameters of this product prior to use should operate this equipment. Personnel working in the laser hazard area must also receive periodic training. This system is intended for use only by physicians trained in the photodynamic treatment of retinal diseases.

Caution: Federal (USA) law restricts to sale by or on the order of a physician.

Caution: Use of controls or adjustments or performance of procedures other than specified here may result in hazardous radiation exposure.

To prevent the risk of electrical shock and exposure to potentially harmful radiation, do not remove the cover. This unit contains no user serviceable parts. If the fuse located on the rear panel should fail, replace it with an identical fuse. If repair is required, contact a factory service representative.

Danger: Do not use in the presence of flammable anesthetic mixture with air, oxygen, or nitrous oxide. Avoid using any other flammable or fume-emitting substances in the operational field.

Note: There are no user serviceable parts inside this unit. Opening this unit or adjusting components inside the unit will void the warranty since such actions may compromise the performance and / or safety of the laser system.

Iridex, Inc., 515 Shaker Rd., East Longmeadow, MA 01028 USA
Telephone: 413 565 0600 Fax: 413 565 0611

Only the treating physician aiming the laser beam should have access to the laser footswitch. Make sure the footswitch depressed is the correct one to avoid accidental laser exposure.

SAFETY PRECAUTIONS

The Ceralas™ I semiconductor Diode laser is a Class IIIb laser according to EN 60825-1 and EN 60601-2-22. A Class IIIb laser is hazardous to the eye from either the direct beam or diffuse or scattered reflections. The beam also represents a significant skin and fire hazard.

AVOID EYE OR SKIN EXPOSURE TO DIRECT OR SCATTERED RADIATION. TAKE ALL NECESSARY PROTECTIVE MEASURES IN THE AREAS WHERE THE LASER IS BEING USED.

Owners and operators are responsible for ensuring that their facility uses the Ceralas™ in accordance with the measures outlined in the American National Standard for the Safe Use of Lasers in Health Care Facilities (**ANSI Z 136.3 -1996 and ANSI Z 136.1 - 1993**), in consultation with their Laser Safety Officer.

These measures include: personnel training and supervision, proper access control to the controlled laser zone (treatment room), beam containment within the controlled laser zone using screens, barriers, and minimizing unprotected exposure with protective eyewear, clothing, and door interlocks. The laser hazard area should be clearly marked with appropriate signage. Ensure entrance to the area is closed before operating the system.

Circuitry for connection of a remote interlock is provided. The interlock can be attached to contacts on the laser room door. If the interlock circuit is broken, light delivery will be discontinued or disabled. This prevents the laser system from firing if the laser room is entered during use.

Do not operate the system with frayed or faulty cords or fibers, or if the system appears to be malfunctioning shut the unit down, remove the key, unplug it, and post a sign stating that the machine is out of order. Contact Biolitec for repairs.

Power density and spot size largely determines the degree of interaction of the laser beam with tissue. The system will automatically calculate the energy dose parameters to be delivered to the retina, based on the input spot size and power density values. For safe and effective use it is imperative that the input treatment parameter values are correct, (e.g. magnification values match the lens), and that the spot size is only as large as is necessary.

EYE INJURY

Visible light (689 nm) from the Ceralas™ I passes through the transparent components of the eye and is focused on the retina at the back of the eye. The optical output power from this laser can cause severe eye damage or other injuries.

ALL PERSONNEL OTHER THAN THE OPERATOR MUST WEAR PROTECTIVE EYE WEAR TO ELIMINATE THE RISK OF EYE DAMAGE

Glasses should be designed for protection from Continuous Wave laser radiation at a wavelength of 689 nm. Optical density of the glasses has to be greater than 2.0, and should be resistant to photobleaching. Glasses not designed to meet this requirement, (possibly including those supplied with other laser systems) are not suitable for eye protection. Appropriate protective glasses are available from your Biolitec representative.

DO NOT STARE INTO AIMING BEAM OR VIEW IT DIRECTLY THROUGH OPTICAL INSTRUMENTS. AVOID DIRECT EXPOSURE TO THE AIMING BEAM. AVOID PLACING REFLECTIVE MATERIAL SUCH AS METALS AND GLASS INTO THE BEAM.

DO NOT USE FLAMMABLE OR EXPLOSIVE ANESTHETIC GASSES THAT MAY BE IGNITED BY THE LASER. AVOID USING OTHER FLAMMABLE OR FUME-EMITTING SUBSTANCES IN THE OPERATIVE FIELD.

The user should read and be thoroughly familiar with this manual before operating the instrument and keep it nearby for easy reference. The equipment should be routinely inspected and maintained in accordance with the instructions given in the Maintenance section of this manual. Biolitec is not responsible for injury caused by misuse, poor care or maintenance of the laser system.

Accidental irradiation to other than the target tissue may result in **laser burn**.

Nominal Ocular Hazard Distance (NOHD) is 0.4 m from the distal end of the fiber.

NOTE: To protect against unauthorized use, remove the key from the key switch when the system is not in use.

For service needs, or if you notice a change in laser efficacy, please contact Biolitec.

EXPLANATION OF SYMBOLS USED

Warning – This symbol is intended to alert the user to the presence of important operating/safety instructions in the literature accompanying the laser.

Emergency Laser Off – Power to Laser has been stopped.

Laser Warning – Laser energy is generated here.

Protective Earth (Ground) – Ground connection is made here.

| — **On (Power: Connection to mains)**

O — **Off (Power: Disconnection to the mains)**

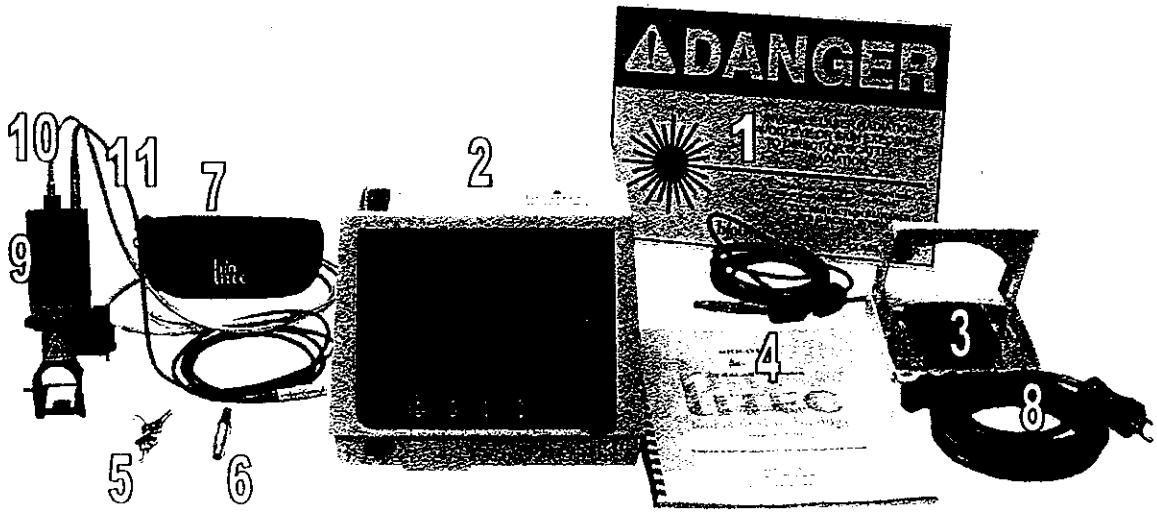
Caution High Voltage – High Voltage is generated here.

~ — **Alternating Current Symbol**

Type B Equipment – Equipment is classified as Type B

Bioflex, Inc., 515 Shaker Rd., East Longmeadow, MA 01028 USA
Telephone: 413.525.0600 Fax: 413.525.0611

PARTS LIST



1. Danger Sign
2. Ceralas I 689nm Laser
3. Foot Switch
4. User's Manual
5. Keys
6. Remote Interlock
7. Safety Glasses
8. Power Cord
9. Ceralink™ Slit Lamp Adapter (SLA)
10. Fiber Jumper Cable
11. SLA Control Cable

PRODUCT DESCRIPTION

Intended Use

The Ceralas™ I laser system and the Ceralink Slit Lamp Adapter is intended to be a light source for the photoactivation of the light activated drug VISUDYNE® (verteporfin for injection) in photodynamic therapy for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. It has an optical output power of 0.5 W maximum at a wavelength of 689 nm. Refer to the Visudyne® package insert for information and instructions on use of the drug and information on the laser treatment parameters.

Laser System

The laser system consists of a 689 nm 0.5 W Laser, a Ceralink™ Slit Lamp Adapter (SLA), and a fiber optic cable connecting the laser to the Slit Lamp Adapter.

Light path

The optical radiation is produced by a semiconductor diode laser. The diodes are fabricated from Indium Gallium Arsenide (InGaAs) semiconductor diodes that generate visible laser radiation. Electrical energy is applied to the diodes to produce optical output. The radiation from the diodes is coupled into optical fibers. The diodes and coupling take place in a hermetically sealed housing to prevent the diodes from experiencing degradation due to environmental conditions. The coupled radiation is carried via the optical fibers to the optics module. Within the optics module, the radiation is focused by a pair of lenses into the fiber optic cable connecting the laser to the Ceralink™ Slit Lamp Adapter.

The fiber optic jumper cable contains an optical mode mixing element on one end, and at the Ceralink™ Slit Lamp Adapter end, a lens for the purpose of uniform light distribution into the Slit Lamp Adapter (uniform = at any point of the spot coming from the fiber, the power density is the same). A collimating lens in the Slit Lamp Adapter produces a spot size of 5 mm on an adjustable iris. The iris is modulated by a stepper motor in the range from 1 to 5 mm. The light passes through the iris and is focused through a second lens which produces an image of the iris in the focus plane of the slit lamp. This light is reflected off a mirror which is 99.9% reflective for 689 nm light, and 50% reflective for 635 nm light into the target. This type of mirror offers the user protection from the 689 nm energy and allows the aiming beam to still be seen.

Control

The laser is controlled by an embedded computer. The computer is responsible for reading the user input and controlling the safety systems and power delivery. User input is done via a key pad, multi-function knob and foot switch.

The remote interlock and fiber interlock are polled by the computer and return the laser to standby in the event of a fault. Optical output power is controlled by an analog constant laser power circuit. (closed loop laser driver). The set point for the power is calculated from the calibration file which is a part of the laser software and forwarded to the laser driver as an analog voltage level. The computer monitors the laser power using an additional independent power monitor circuit and a photodiode within the hermetically sealed diode module. If the power falls out of the specified range (± 10% tolerance band) the computer returns the laser to standby. A watchdog timer ensures that the computer is operating properly. The time is controlled using two independent timers. The wavelength is governed by the temperature of the diodes. A temperature control module measures the temperature of the diodes and maintains the temperature by controlling the current to the thermoelectric cooler closed loop circuit.

The Ceralink™ Slit Lamp Adapter is connected to the Laser via an RS232 link and an optical cable. Starting the laser system resets the microcontroller inside the slit lamp and restarts the slit lamp software. The microcontroller tests the iris position and adjusts the iris to a predefined start position. The SL microcontroller is working as a slave and talks with the master – laser computer - via an RS232 interface using a serial interface protocol. The exchange of information via the RS232 is a clear standard and the master knows the position of the iris at any time.

WARNING- The laser MUST only be used with the Ceralink™ Slit Lamp Adaptor in conjunction with either a Zeiss or Haag-Streit slit lamp.

SYSTEM PERFORMANCE

0.5 Watts optical output power are delivered through a 400 um core, 0.37 N.A. fiber, fitted with an SMA-905 fiber connector; at a nominal wavelength of 689 nm. The Ceralink™ Slit Lamp Adapter delivers spot sizes between 1 mm and 5 mm. Depending on the contact lens used, spot sizes up to 8 mm can be reached.

The Ceralas I laser meets the intent of Directive EN 60601-1-2 Part 2: Medical Electrical Equipment, Collateral Standard: Electromagnetic Compatibility dated 1993-05. Compliance was demonstrated to the following specifications as listed: EN 60825-1 (1994+ A11:1996+A2:2001), IEC 60825-1:1993+A2:2001, IEC 60601-1 (1988+A1:1991+A2:1995), IEC 60601-1-1 (1992), and IEC 60601-2-22 (1995).

Biolitec, Inc., 515 Shaker Rd., East Longmeadow, MA 01028 USA
Telephone: 413-525-0600 Fax: 413-525-0611

TECHNICAL SPECIFICATIONS

Laser Type	Semiconductor Diode Laser
Laser Class	IIIb
Wavelength	689 nm ± 3 nm
Numerical Aperture At Fiber Output Port	0.37
Beam Divergence At Output Port	Half angle (ø/2) = 20.5°
Fiber Diameter	400 µm
Power Output	0.5 W (max)
Spot Sizes	1 mm – 8 mm
Power Control	Built in power monitoring circuit
Power Stability	± 10%
Fiber Connector	SMA 905
Aiming Beam	Visible laser diode 635 nm ± 10 nm. Typically 1 mW coaxial with treatment.
Mode of Operation	Continuous
Cooling	Forced air
Electrical Rating	100-120 VAC ~ 50/60 Hz, 65 VA 100-230 VAC ~ 50 Hz, 65 VA
Fuse	2 x 2A Type: Slow Blow
Class of Product	I
Degree of Protection Against Shock	Type B

Biolitec, Inc., 515 Shaker Rd., East Longmeadow, MA 01028 USA
Telephone: 413-525-0600 Fax: 413-525-0611

Degree of Protection Against Harmful Ingress Of Water	Ordinary Equipment
Dimensions	19 cm High x 24 cm Wide x 37 cm Deep
Weight	7 kg (15.4 lbs)
Safety Standards	Complies with: IEC 60601-1, IEC 60601-2-22, IEC 60825-1 IEC 60601-1-2, IEC 60601-1-4, 21 CFR 1040.10, 21 CFR 1040.11
Fiber optic delivery	Jumper cable (core diameter 400µm N.A. 0.37) systems FD400
Operating	
Temperature	10°C to 25°C (50°F to 77°F)
Humidity	30-50% RH, non-condensing
Storage	
Temperature	0°C to 40°C (32°F to 104°F)
Humidity	80% RH, non-condensing
Degree of Safety in Flammable Anesthetic Mixture:	Not suitable for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide.

The Manufacturer may make available upon request, circuit diagrams, component part lists, etc.

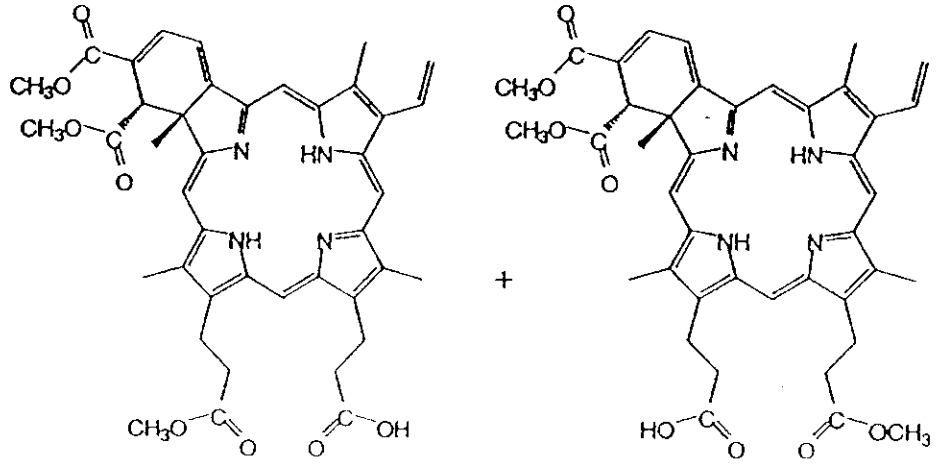
Biolitec, Inc., 515 Shaker Rd., East Longmeadow, MA 01028 USA
Telephone: 413-525-0600 Fax: 413-525-0611

Basis for Approval
4/7/00

VISUDYNE™
(verteporfin for injection)

DESCRIPTION

VISUDYNE™ (verteporfin for injection) is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I and II), represented by the following structures:



I + II

The chemical names for the verteporfin regioisomers are:

9-methyl (I) and 13-methyl (II) *trans*-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*, 25*H*-benzo[*b*]porphine-9,13-dipropanoate

The molecular formula is $C_{41}H_{42}N_4O_8$ with a molecular weight of approximately 718.8.

Each mL of reconstituted VISUDYNE contains:

ACTIVE: Verteporfin, 2 mg

INACTIVES: Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate and butylated hydroxytoluene

CLINICAL PHARMACOLOGY

Mechanism of Action

VISUDYNE therapy is a two-stage process requiring administration of both verteporfin for injection and nonthermal red light.

Verteporfin is transported in the plasma primarily by lipoproteins. Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase (leukotriene) and cyclo-oxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction. Verteporfin appears to somewhat preferentially accumulate in neovasculature, including choroidal neovasculature. However, animal models indicate that the drug is also present in the retina. Therefore, there may be collateral damage to retinal structures following photoactivation including the retinal pigmented epithelium and outer nuclear layer of the retina. The temporary occlusion of choroidal neovascularization (CNV) following VISUDYNE therapy has been confirmed in humans by fluorescein angiography.

Pharmacokinetics

Following intravenous infusion, verteporfin exhibits a bi-exponential elimination with a terminal elimination half-life of approximately 5-6 hours. The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m^2. At the intended dose, pharmacokinetic parameters are not significantly affected by gender.

Verteporfin is metabolized to a small extent to its diacid metabolite by liver and plasma esterases. NADPH-dependent liver enzyme systems (including the cytochrome P450 isozymes) do not appear to play a role in the metabolism of verteporfin. Elimination is by the fecal route, with less than 0.01% of the dose recovered in urine.

In a study of patients with mild hepatic insufficiency (defined as having two abnormal hepatic function tests at enrollment), AUC and C_{max} were not significantly different from the control group, half-life however was significantly increased by approximately 20%.

Clinical Studies

Two adequate and well-controlled, double-masked, placebo-controlled, randomized studies were conducted in patients with classic-containing subfoveal CNV secondary to age-related macular degeneration. A total of 609 patients (VISUDYNE 402, placebo 207) were enrolled in these two studies. A planned analysis of safety and efficacy was conducted at 1 year, with 94% of patients completing that portion of the study. During these studies, retreatment was allowed every 3 months if fluorescein angiograms showed any recurrence or persistence of leakage. The placebo control (sham treatment) consisted of intravenous administration of Dextrose 5% in Water, followed by light application identical to that used for VISUDYNE therapy.

The difference between treatment groups statistically favored VISUDYNE at the 1-year analysis for visual acuity endpoints.

The subgroup of patients with predominantly classic CNV lesions was more likely to exhibit a treatment benefit (N=243; VISUDYNE 159, placebo 84). Predominantly classic CNV lesions were defined as those in which the classic component comprised 50% or more of the area of the entire lesion. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of 28% between treatment groups (67% for VISUDYNE patients compared to 39% for placebo patients, $P<.001$). Severe vision loss (≥6 lines of visual acuity from baseline) was experienced by only 12% of VISUDYNE-treated patients compared to 33% of placebo-treated patients.

Patients with predominantly classic CNV lesions that did not contain occult CNV exhibited the greatest benefit (N=134; VISUDYNE 90, placebo 44). These patients demonstrated a 49% difference between treatment groups when assessed by the <3 lines-lost definition (77% vs. 27%). Severe vision loss (≥6 lines of visual acuity from baseline) was experienced by only 10% of VISUDYNE-treated patients compared to 41% of placebo-treated patients.

Older patients (≥75 years), patients with dark irides, patients with occult lesions or patients with less than 50% classic CNV were less likely to benefit from VISUDYNE therapy.

The safety and efficacy of VISUDYNE beyond 2 years have not been demonstrated.

INDICATIONS AND USAGE

VISUDYNE therapy is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

CONTRAINDICATIONS

VISUDYNE is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation.

WARNINGS

Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of VISUDYNE could result in incomplete treatment due to partial photoactivation of VISUDYNE, overtreatment due to overactivation of VISUDYNE, or damage to surrounding normal tissue.

PRECAUTIONS

General

Standard precautions should be taken during infusion of VISUDYNE to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing intravenous (IV) line should be established before starting VISUDYNE infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

If extravasation does occur, the infusion should be stopped immediately and cold compresses applied (see Warnings).

VISUDYNE therapy should be considered carefully in patients with moderate to severe hepatic impairment since there is no clinical experience with verteporfin in such patients.

There is no clinical data related to the use of VISUDYNE in anesthetized patients. At a >10-fold higher dose given by bolus injection to anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious pigs or in any other species, whether conscious or under general anesthesia.

Information for Patients

Patients who receive VISUDYNE will become temporarily photosensitive after the infusion. Patients should wear a wrist band to remind them to avoid direct sunlight for 5 days. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. Sources of bright light include, but are not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices.

If treated patients must go outdoors in daylight during the first 5 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Drug Interactions

Drug interaction studies in humans have not been conducted with VISUDYNE.

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of VISUDYNE therapy. Possible examples include the following:

Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of VISUDYNE uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide, diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β-carotene, ethanol, formate and mannitol, would be expected to decrease VISUDYNE activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could also decrease the efficacy of VISUDYNE therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of verteporfin.

Photodynamic therapy (PDT) as a class has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

No effect on male or female fertility has been observed in rats following intravenous administration of verteporfin for injection up to 10 mg/kg/day (approximately 60 and 40 fold human exposure at 6 mg/m^2 based on AUC_{inf} in male and female rats, respectively).

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Rat fetuses of dams administered verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis (approximately 40 fold human exposure at 6 mg/m^2 based on AUC_{inf} in female rats) exhibited an increase in the incidence of anophthalmia/microphthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125 fold the human exposure at 6 mg/m^2 based on AUC_{inf} in female rats) had an increased incidence of wavy ribs and anophthalmia/microphthalmia.

In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7 fold human exposure at 6 mg/m^2 based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. VISUDYNE should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether verteporfin for injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VISUDYNE is administered to a women who is nursing.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Approximately 90% of the patients treated with VISUDYNE in the clinical efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

ADVERSE REACTIONS

The most frequently reported adverse events to VISUDYNE are headaches, injection site reactions (including extravasation and rashes) and visual disturbances (including blurred vision, decreased visual acuity and visual field defects). These events occurred in approximately 10-20% of patients. The following events, listed by Body System, were reported more frequently with VISUDYNE therapy than with placebo therapy and occurred in 1-10% of patients:

Ocular Treatment Site:	Cataracts, conjunctivitis/conjunctival injection, dry eyes, ocular itching, severe vision loss, subconjunctival, subretinal or vitreous hemorrhage
Body as a Whole:	Asthenia, back pain (primarily during infusion), fever, flu syndrome, photosensitivity
Cardiovascular:	Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins
Dermatologic:	Eczema

Digestive:	Constipation, gastrointestinal cancers, nausea
Hemic and Lymphatic:	Anemia, white blood cell count decreased, white blood cell count increased
Hepatic:	Elevated liver function tests
Metabolic/Nutritional:	Albuminuria, creatinine increased
Musculoskeletal:	Arthralgia, arthrosis, myasthenia
Nervous system:	Hypesthesia, sleep disorder, vertigo
Respiratory:	Pharyngitis, pneumonia
Special Senses:	Decreased hearing, diplopia, lacrimation disorder
Urogenital:	Prostatic disorder

Severe vision decrease, equivalent of 4 lines or more, within 7 days after treatment has been reported in 1-4% of patients. Partial recovery of vision was observed in many patients. Photosensitivity reactions occurred in the form of skin sunburn following exposure to sunlight. The higher incidence of back pain in the VISUDYNE group occurred primarily during infusion.

OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

DOSAGE AND ADMINISTRATION

A course of VISUDYNE therapy is a two-step process requiring administration of both drug and light.

The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with light from a nonthermal diode laser.

The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.

Lesion Size Determination

The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

Spot Size Determination

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

VISUDYNE Administration

Reconstitute each vial of VISUDYNE with 7 mL of sterile Water for Injection to provide 7.5 mL containing 2 mg/mL. Reconstituted VISUDYNE must be protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution.

The volume of reconstituted VISUDYNE required to achieve the desired dose of 6 mg/m^2 body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump and in-line filter.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (See Precautions).

Light Administration

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10-minute infusion with VISUDYNE.

Photoactivation of VISUDYNE is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm^2 of neovascular lesion administered at an intensity of 600 mW/cm^2. This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation.

The laser system must deliver a stable power output at a wavelength of 689±3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

The following laser systems have been tested for compatibility with VISUDYNE and are approved for delivery of a stable power output at a wavelength of 689±3 nm:

Coherent Opal Photoactivator Laser Console and LaserLink Adapter,
Manufactured by Coherent, Inc., Santa Clara, CA

Zeiss VISULAS 690s laser and VISULINK PDT adapter,
Manufactured by Carl Zeiss Inc., Thornwood, NY

Concurrent Bilateral Treatment

The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous VISUDYNE therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior VISUDYNE therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues are identified, the second eye can be treated using the same treatment regimen after a second VISUDYNE infusion. Approximately 3 months later, both eyes can be evaluated and concurrent

treatment following a new VISUDYNE infusion can be started if both lesions still show evidence of leakage.

HOW SUPPLIED

VISUDYNE is supplied in a single use glass vial with a gray bromobutyl stopper and aluminum flip-off cap. It contains a lyophilized cake with 15 mg verteporfin. The product is intended for intravenous injection only.

Spills and Disposal

Spills of VISUDYNE should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is recommended. All materials should be disposed of properly.

Accidental Exposure

Because of the potential to induce photosensitivity reactions, it is important to avoid contact with the eyes and skin during preparation and administration of VISUDYNE. Any exposed person must be protected from bright light (See Warnings).

NDC 58768-150-15

Store VISUDYNE between 20°C and 25°C (68°F-77°F).

Rx Only

Manufactured by:

Parkedale Pharmaceuticals, Inc.
Rochester, MI 48307

For:

QLT PhotoTherapeutics, Inc.
Seattle, WA 98101

Co-developed and Distributed by:

CIBA Vision
A Novartis Company
Duluth, GA 30097